

## Complete Summary

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### GUIDELINE TITLE

Pharmacologic treatment of low bone density or osteoporosis to prevent fractures: a clinical practice guideline from the American College of Physicians.

### BIBLIOGRAPHIC SOURCE(S)

Qaseem A, Snow V, Shekelle P, Hopkins R Jr, Forciea MA, Owens DK, Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Pharmacologic treatment of low bone density or osteoporosis to prevent fractures: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2008 Sep 16;149(6):404-15. [155 references] [PubMed](#)

### GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT

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## SCOPE

### DISEASE/CONDITION(S)

- Low bone density
- Osteoporosis
- Osteoporotic fractures (vertebral, nonvertebral, and hip fractures)

### GUIDELINE CATEGORY

Prevention  
Risk Assessment  
Treatment

## **CLINICAL SPECIALTY**

Family Practice  
Geriatrics  
Internal Medicine  
Obstetrics and Gynecology  
Preventive Medicine

## **INTENDED USERS**

Advanced Practice Nurses  
Nurses  
Physician Assistants  
Physicians

## **GUIDELINE OBJECTIVE(S)**

To synthesize the evidence for the following questions:

1. What are the comparative benefits in fracture reduction among and also within the following treatments for low bone density: bisphosphonates, specifically alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid; calcitonin; estrogen for women; teriparatide; selective estrogen receptor modulators (SERMs), specifically raloxifene and tamoxifen; testosterone for men; vitamins and minerals, specifically vitamin D and calcium; and the combination of calcium plus vitamin D?
2. How does fracture reduction resulting from treatments vary among individuals with different risks for fracture as determined by bone mineral density (borderline, low, or severe), previous fractures (prevention vs. treatment), age, sex, glucocorticoid use, and other factors (such as community-dwelling vs. institutionalized or vitamin D-deficient vs. not)?
3. What are the short- and long-term harms (adverse effects) of these therapies, and do these vary by specific subpopulations?

## **TARGET POPULATION**

All adult men and women with low bone density or osteoporosis

## **INTERVENTIONS AND PRACTICES CONSIDERED**

### **Pharmacologic Treatment of Low Bone Density to Prevent Fractures**

1. Bisphosphonates
  - Alendronate
  - Etidronate
  - Ibandronate
  - Pamidronate
  - Risedronate
  - Zoledronic acid
2. Calcitonin

3. Estrogen
4. Teriparatide
5. Selective estrogen receptor modulators (SERMs)
  - Raloxifene
  - Tamoxifen
6. Testosterone
7. Calcium and vitamin D

## **MAJOR OUTCOMES CONSIDERED**

- Bone density and T-score
- Vertebral, nonvertebral, and hip fracture rates
- Adverse drug effects

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Searches of Electronic Databases

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

The literature search included studies from MEDLINE (1966 to December 2006), the *ACP Journal Club* database, the Cochrane Central Register of Controlled Trials (no date limits), the Cochrane Database of Systematic Reviews (no date limits), Web sites of the United Kingdom National Institute of Health and Clinical Excellence (no date limits), and the United Kingdom Health Technology Assessment Program (January 1998 to December 2006). The reviewers limited their search to English-language publications and human studies. They derived evidence for comparative benefits of various treatments exclusively from randomized, controlled trials, whereas they included evidence from other types of studies for short- and long-term harms.

### **NUMBER OF SOURCE DOCUMENTS**

This guideline is based on an evaluation of 76 randomized, controlled trials, 4 of which were identified in the updated search, and 24 meta-analyses that were included in the efficacy analyses. The analyses of adverse events included 491 articles, representing 417 randomized trials, 25 other controlled clinical trials, 11 open-label trials, 31 large observational studies, and 9 case reports of osteonecrosis among bisphosphonate users.

### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Given)

### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

The American College of Physicians (ACP) rates the evidence and recommendations by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system with minor modifications (See "Rating Scheme for the Strength of the Recommendations" field, below).

## **METHODS USED TO ANALYZE THE EVIDENCE**

Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

Two physicians independently abstracted data about study populations, interventions, follow-up, and outcome ascertainment by using a structured form. For each group within a randomized trial, a statistician extracted the sample size and number of persons reporting fractures. Two reviewers, under the supervision of the statistician, independently abstracted information about adverse events. The statistician or the principal investigator resolved disagreements.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus  
Informal Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Guideline developers systematically reviewed the evidence to address the questions stated above.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

<b>American College of Physicians' Guideline Grading System*</b>		
<b>Quality of Evidence</b>	<b>Strength of Recommendation</b>	
	Benefits Clearly Outweigh Risks and Burden <b>OR</b> Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
High	Strong	Weak

American College of Physicians' Guideline Grading System*		
Quality of Evidence	Strength of Recommendation	
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I recommendation	

\*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review  
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was approved by the American College of Physicians (ACP) Board of Regents on 12 May 2008.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The strength of evidence (high, moderate, low, insufficient evidence to determine benefits or risks) and strength of recommendations (strong, weak, I recommendation) are defined at the end of the "Major Recommendations" field.

**Recommendation 1:** American College of Physicians (ACP) recommends that clinicians offer pharmacologic treatment to men and women who have known osteoporosis and to those who have experienced fragility fractures (**Grade: strong recommendation; high-quality evidence**).

Good evidence supports the treatment of patients who have osteoporosis to prevent further loss of bone and to reduce the risk for initial or subsequent fracture. Randomized, controlled trials offer good evidence that, compared with placebo, alendronate, ibandronate, risedronate, calcitonin, teriparatide, and raloxifene prevent vertebral fractures. Evidence is also good that teriparatide

prevents nonvertebral fractures compared with placebo and that risedronate and alendronate prevent both nonvertebral and hip fractures compared with placebo. Estrogen has been shown to be associated with reduced vertebral, nonvertebral, and hip fractures. The evidence on use of calcium with or without vitamin D is mixed, and the effectiveness is modest. Because most trials of other pharmacologic therapy included their use, ACP recommends adding calcium and vitamin D to osteoporosis treatment regimens. Evidence is insufficient to determine the appropriate duration of therapy.

**Recommendation 2:** ACP recommends that clinicians consider pharmacologic treatment for men and women who are at risk for developing osteoporosis **(Grade: weak recommendation; moderate-quality evidence)**.

Evidence supports the treatment of selected patients who are at risk for osteoporosis but who do not have a T-score on dual x-ray absorptiometry (DXA) less than -2.5. Evidence supporting preventive treatment is stronger for patients who are at moderate risk for osteoporosis, which includes patients who have a T-score from -1.5 to -2.5, are receiving glucocorticoids, or are older than 62 years of age.

Factors that increase the risk for osteoporosis in men include age (>70 years), low body weight (body mass index <20 to 25 kg/m<sup>2</sup>), weight loss (>10% [compared with the usual young or adult weight or weight loss in recent years]), physical inactivity (no physical activities performed regularly, such as walking, climbing stairs, carrying weights, housework, or gardening), corticosteroid use, and androgen deprivation therapy. Risk factors for women include lower body weight, the single best predictor of low bone mineral density; smoking; weight loss; family history; decreased physical activity; alcohol or caffeine use; and low calcium and vitamin D intake. In certain circumstances, a single risk factor (for example, androgen deprivation therapy in men) is enough for clinicians to consider pharmacologic treatment.

Research groups are developing calculators, such as the World Health Organization's Fracture Risk Assessment Tool (available at [www.shef.ac.uk/FRAX/](http://www.shef.ac.uk/FRAX/)), to predict the risk for osteoporotic fracture. Such tools will help guide both clinician and patient decisions.

**Recommendation 3:** ACP recommends that clinicians choose among pharmacologic treatment options for osteoporosis in men and women on the basis of an assessment of risk and benefits in individual patients **(Grade: strong recommendation; moderate-quality evidence)**.

ACP recommends that the choice of therapy for patients who are candidates for pharmacologic treatment be guided by judgment of the risks, benefits, and adverse effects of drug options for each individual patient. Table 2 in the original guideline document summarizes the benefits and harms of pharmacologic agents for fracture risk. Because good-quality evidence shows that bisphosphonates reduce the risk for vertebral, nonvertebral, and hip fractures, they are reasonable options to consider as first-line therapy, particularly for patients who have a high risk for hip fracture. Evidence from head-to-head trials is insufficient to demonstrate the superiority of one bisphosphonate over another. Alendronate and risedronate have been studied more than other bisphosphonates (see Table 2 in

the original guideline document). Ibandronate has not been shown to reduce nonvertebral or hip fractures, which may be an important consideration for some patients. In a recent trial, zoledronic acid administered to patients with a recent hip fracture reduced subsequent fracture and improved survival. Of the other agents available for treatment of osteoporosis, estrogen has efficacy for vertebral, nonvertebral, and hip fractures but is associated with other serious risks; calcitonin has not been demonstrated to reduce nonvertebral and hip fractures; and calcium and vitamin D are part of the treatment regimen in most studies of pharmacologic agents for osteoporosis.

Refer to the "Potential Harms" field of this summary for a discussion of adverse effects and other risks of pharmacologic therapy.

See the original guideline document for recommendations for further research.

**Definitions:**

<b>American College of Physicians' Guideline Grading System*</b>		
<b>Quality of Evidence</b>	<b>Strength of Recommendation</b>	
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Insufficient evidence to determine net benefits or risks	I recommendation	

\*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

**CLINICAL ALGORITHM(S)**

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized, controlled trials, meta-analyses, other controlled clinical trials, open-label trials, observational studies, and case reports.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Prevention of further loss of bone and reduction of the risk for initial or subsequent fracture

### POTENTIAL HARMS

#### Adverse Effects Associated with Various Medications

Oral bisphosphonates increase the risk for such gastrointestinal adverse events as acid reflux. However, pooled analyses showed no differences in occurrence of mild upper gastrointestinal events among alendronate, ibandronate, risedronate, or zoledronic acid versus placebo; however, pooled analyses of 18 trials of etidronate versus placebo indicated an increased risk for mild gastrointestinal events. The evidence linking zoledronic acid infusion with atrial fibrillation is contradictory. Raloxifene increased the pooled risk for pulmonary embolism and thromboembolic events. Estrogen was linked to an increased risk for cerebrovascular and thromboembolic events. Testosterone has well-known side effects.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All American College of Physicians (ACP) clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.
- The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.



## IMPLEMENTATION TOOLS

Patient Resources  
Staff Training/Competency Material

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness  
Staying Healthy

### IOM DOMAIN

Effectiveness  
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Qaseem A, Snow V, Shekelle P, Hopkins R Jr, Forciea MA, Owens DK, Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Pharmacologic treatment of low bone density or osteoporosis to prevent fractures: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2008 Sep 16;149(6):404-15. [155 references] [PubMed](#)

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2008 Sep 16

### GUIDELINE DEVELOPER(S)

American College of Physicians - Medical Specialty Society

### SOURCE(S) OF FUNDING

American College of Physicians

### GUIDELINE COMMITTEE

Clinical Efficacy Assessment Subcommittee of the American College of Physicians

## **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

Employment: R. Hopkins (University of Arkansas). Consultancies: D.K. Owens (GE Healthcare). Grants received: V. Snow (Novo Nordisk, United Healthcare Foundation, Centers for Disease Control and Prevention, Atlantic Philanthropies). Any conflict of interest of the Guideline Development Committee group members was declared, discussed, and resolved.

## **GUIDELINE STATUS**

This is the current release of the guideline.

## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [American College of Physicians \(ACP\) Web site](#).

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following is available:

- Prevention and treatment of osteoporosis. Continuing medical education (CME) course. Available from [Annals of Internal Medicine Web site](#).

## **PATIENT RESOURCES**

The following is available:

- Summaries for patients. Drug treatment for low bone density or osteoporosis to prevent fractures: a clinical practice guideline from the American College of Physicians.

Electronic copies: Available in Portable Document Format (PDF) from the [Annals of Internal Medicine Web site](#).

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

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## **NGC STATUS**

This NGC summary was completed by ECRI on January 12, 2009. The information was verified by the guideline developer on January 23, 2009.

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